REMARKS

The Present Invention

The present invention is directed to a method of inhibiting the binding of a chaperone protein with its client protein or client polypeptide by contacting a chaperone protein with a coumarin or coumarin derivative, wherein the chaperone protein is heat shock protein Hsp90.

The Pending Claims

Claims 1, 3-17, and 22 are currently pending. Claims 1, 3-17, and 22 are directed to a method of inhibiting a chaperone protein with its client protein or client polypeptide by contacting a chaperone protein with a coumarin or a coumarin derivative, wherein the chaperone protein is Hsp90.

Amendments to the Claims

Claim 6 has been amended to correctly identify the independent claim (claim 1) from which claim 6 depends.

The Office Action

Claims 1, 8-15, and 22 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Omarbasha et al. (*Cancer Res.*, 49, 3045-3049 (1989)) as evidenced by Prodromou et al. Claims 1, 3, 5-15 and 22 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Eder et al. (*Cancer Res.*, 49, 595-598 (1989)) as evidenced by Prodromou et al. Claims 1, 3-6, 12-15, and 22 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Schneider et al. (*Proc. Natl. Acad. Sci.*, 93: 14536-14541 (1996)) in view of Gormley et al.(*Biochem.*,35, 5083-5092 (1996)) and Prodromou et al.(*Cell*, 90, 65-75 (1997)). Claims 8-11 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Schneider et al., Gormley et al., Prodromou et al., and in further view of Schulte et al. (*Biochem. and Biophys. Res. Comm.*,239, 655-659 (1997)). Claims 16 and 17 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Schneider et al., Gormley et al., Prodromou et al. in further view of Hu et al. (*Proc. Natl. Acad. Sci.*, 93: 1060-1064 (1996)).

Discussion of Rejection Under 35 U.S.C. § 102(b)

Claims 1, 8-15 and 22 have been rejected as allegedly anticipated by Omarbasha et al. as evidenced by Prodromou et al. The Office contends that Omarbasha et al. inherently discloses a method of inhibiting binding of Hsp90 with its client protein or client polypeptide, wherein the method comprises contacting Hsp90 with coumarin or a coumarin derivative, such that the

coumarin or coumarin derivative binds Hsp90, which binding inhibits Hsp90 from binding its client protein or client polypeptide. Furthermore, the Office contends that the inhibition of binding between Hsp90 and a client polypeptide such as serine/threonine Raf-1, tyrosine kinase $p185^{erbB2}$, and mutant p-53 is inherently disclosed in Omarbasha et al. The Office also alleges that Omarbasha et al. inherently discloses that a client protein or client polypeptide is inactive, and in some instances, degraded, subsequent to the binding of Hsp90 to coumarin or a coumarin derivative. Finally, the Office alleges that Omarbasha et al. inherently discloses that the binding of coumarin or a coumarin derivative to Hsp90 inhibits cellular proliferation, specifically in the context of cancer. Applicants respectfully traverse the rejections.

Omarbasha et al. is directed to the injection of coumarin in to rats to decrease prostate tumor size. Omarbasha et al. does not teach that coumarin or a coumarin derivative is localized to Hsp90, nor does Omarbasha et al. teach that coumarin or a coumarin derivative contact Hsp90 in order to inhibit binding of Hsp90 to its client protein/polypeptide. There is no disclosure in Omarbasha et al. from which it can be inferred that necessarily prostate tumor size is affected post coumarin administration by contacting coumarin or a coumarin derivative with Hsp90. Further, while it is known that coumarin has an effect on various types of cells or proteins, as recited in Omarbasha et al. (*See* Abstract), it is simply an unsubstantiated assumption that the effects of coumarin described in Omarbasha et al. are related to any relationship between coumarin, Hsp90, and its client protein/polypeptide.

It is undisputed that Omarbasha et al. does not *explicitly* disclose all the limitations of the rejected claims, including contacting of Hsp90 with coumarin or a coumarin derivative. While the disclosure of a claim limitation can be inherent, rather than explicit, in a reference, the disclosure of limitations in a reference may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to establish the inherent disclosure of that thing. Inherency must be established as a necessary consequence of what was intended. *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1366, 52 U.S.P.Q.2d 1303, 1305 (Fed. Cir. 1999).

Omarbasha et al. does not anticipate the subject claims explicitly or inherently because Omarbasha et al. teaches only the administration of coumarin to rats. There is no disclosure of the claimed methods requiring coumarin or a coumarin derivative to contact Hsp90 such that Hsp90's client protein(s)/polypeptide(s) are inhibited from binding with Hsp90, nor can it be said that the mere administration of coumarin or a coumarin derivative will necessarily result in such contact as required by the claimed methods. In other words, by administering coumarin to rats in accordance with the disclosure of Omarbasha et al., it does not necessarily follow that coumarin is contacted with Hsp90, to inhibit the binding of Hsp90 with its client protein/polypeptide. Therefore, the concept of inherency is not applicable here.

The Office cites to Prodromou et al. as evidence that Omarbasha et al. anticipates the subject claims. However, Prodromou et al. does not provide the requisite support since it only teaches that geldanamycin acts by blocking the ATP binding site on Hsp90. Prodromou et al. does not disclose the administration of coumarin or a coumarin derivative, nor does Prodromou et al. disclose the contact of an administered coumarin or coumarin derivative to Hsp90, in order to inhibit the binding of Hsp90 to its client protein/polypeptide.

In view of the above, Applicants respectfully request the withdrawal of the Section 102 rejection of claims 1, 8-15 and 22.

Claims 1, 3, 5-15 and 22 have been rejected as allegedly anticipated by Eder et al. The Office contends that Eder et al. inherently discloses a method of inhibiting binding of Hsp90 with its client protein or client polypeptide, wherein the method comprises contacting Hsp90 with coumarin or a coumarin derivative, such that the coumarin or a coumarin derivative binds Hsp90, which binding inhibits Hsp90 from binding its client protein or client polypeptide. Furthermore, the Office contends that Eder et al. specifies that the coumarin derivative is novobiocin, which has the effect of increasing the rate at which tumor cells are killed. Similar to the analysis above with respect to Omarbasha et al., the disclosure of Eder et al. is different from the claimed methods in at least one material respect. Eder et al. is directed to the combinatorial treatment of novobiocin and alkylating agents to mice implanted with subcutaneous fibrosarcoma. Eder et al. does not teach or suggest that novobiocin alone is administered so as to be localized near Hsp90, let alone that it is administered so as to contact Hsp90, in order to inhibit binding of Hsp90 to its client protein/polypeptide, eventually affecting tumor cell killing post novobiocin administration. The fact that Eder et al. discloses a method of administering novobiocin in conjunction with another compound precludes the very inference of inherency since it cannot be shown that following Eder et al. that the alkylating agent is not responsible for killing the tumor. Specifically, the alkylating agents in conjunction with novobiocin may be the cause of tumor killing.

Accordingly, there is no basis upon which to conclude that Eder et al. inherently anticipates the subject claims given Eder et al. teaches only the administration of novobiocin in combination with alkylating agents to mice. Thus, the claimed method is not an inherent result (i.e., and inevitable or necessary consequence) of what is disclosed in Eder et al.

The Office cites to Prodromou et al. as evidence that Eder et al. anticipates the subject claims. However, Prodromou et al. does not provide the requisite support since it only teaches that geldanamycin acts by blocking the ATP binding site on Hsp90. Prodromou et al. does not disclose the administration of coumarin or a coumarin derivative, nor does Prodromou et al. disclose the contact of an administered coumarin or coumarin derivative to Hsp90, in order to inhibit the binding of Hsp90 to its client protein/polypeptide.

In view of the above, Applicants respectfully request the withdrawal of the Section 102 rejection of claims 1, 3, 5-15 and 22.

Discussion of Rejection Under 35 U.S.C. § 103(a)

Claims 1, 3-6, 12-15, and 22 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Schneider et al. in view of Gormley et al. and Prodromou et al. The Office contends that Schneider et al. teaches a method of inhibiting the binding of heat shock protein Hsp90 with its client protein by contacting Hsp90 with geldanamycin, *in vivo* and in cell extract. The Office also contends that Prodromou et al. teaches that the binding site for geldanamycin on Hsp90 is the same as that of the ATP-binding site on Hsp90, and that Hsp90 is a chaperone for a wide range of client proteins, including client proteins involved in cell proliferation and tumor progression. Further, the Office contends that Gormley et al. teaches that the ATP-binding site of DNA gyrase B protein is the binding site for coumarin and coumarin derivatives, wherein such derivatives comprise chlorobiocin or coumermycin A1 and novobiocin. To conclude this rejection, the Office contends that one of ordinary skill in the art would have been motivated to combine the teachings of Schneider et al., Prodromou et al., and Gormley et al. to reach the claimed methods. This rejection is respectfully traversed.

Applicants note that the Office bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. The appropriate test to establish a *prima facie* case of obviousness demands that the Office satisfy three requirements: (1) the Office must identify some suggestion or motivation, either in the references relied upon or in the knowledge generally available in the art, to modify the references or to combine the reference teachings in such a way as to arrive at the invention claimed, (2) there must be a reasonable expectation of success, and (3) the prior art references relied upon must teach or suggest all of the elements of the claim. *See In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). The Office has not met its burden in establishing a *prima facie* case of obviousness on this basis alone.

First, the Office has not pointed to any teaching or suggestion in the cited references or the relevant art that would render obvious the subject matter of claims 1, 3-6, 12-15, and 22. The Office merely makes an unsupported conclusion that a person having ordinary skill in the art would have been motivated to combine the teachings of the cited references to reach the claimed methods. In fact, the references relied upon by the Office do not provide any suggestion or motivation to combine the teachings thereof.

The Office contends that Schneider et al. discloses that Hsp90 is inhibited by geldanamycin. However, as the instant specification points out, the use of geldanamycin is not entirely satisfactory due to the *in vivo* toxicity of geldanamycin unrelated to its Hsp90

antagonism at, for example, page 2, lines 7-8. Moreover, there is no disclosure whatsoever in Schneider et al. of coumarin or a coumarin derivative. Accordingly, one skilled in the art would not be led by the disclosure of geldanamycin in Schneider et al. to the use of coumarin or a coumarin derivative as is claimed in the present claims.

The Office's conclusion of obviousness is based only on the impermissible hindsight combination of diverse references using Applicant's disclosure as a guide. Specifically, the Office alleges that Schneider et al. teaches a geldanamycin binding site on Hsp90, and Prodromou et al. teaches that the geldanamycin binding site on Hsp90 also binds ATP, and this ATP binding site on Hsp90 is homologous to the ATP binding site on another protein, DNA gyrase B, and Gormley et al. teaches that the ATP binding site on DNA gyrase B is a binding site for a coumarin or a coumarin derivative -- leading the Office to conclude that the instant invention is obvious in view of Schneider et al., Prodromou et al., and Gormley et al. The homology of a binding site amongst proteins is merely an indication that the protein sequences are derived from a common ancestor, and that homology does not necessarily indicate the level of identity between two proteins. In fact, such a comparison does not take into account the unique tertiary or quaternary structure of each binding site relative to the respective protein in which the binding site is located. Moreover, Prodromou et al. identifies differences between the structure of the ATP(geldanamycin)-binding site located in the N-terminal domain of Hsp90 when compared to the homologous binding site on DNA gyrase B. *See* Prodromou et al. at p. 70. Accordingly, the Office's contention that binding of coumarin or a coumarin derivative on DNA gyrase B is similar, or has the same binding affinity or functional effect as the binding of a coumarin or a coumarin derivative on Hsp90 is unsubstantiated. Comparisons with the use of geldanamycin and with the use of coumarin or a coumarin derivative would not have been correlated, as suggested by the Office, by those skilled in the art, and thus, those skilled in the art would not have been motivated at the time of filing the instant application to combine the teachings of the cited references as the Office suggests. The Office's reliance on information gleaned by Applicant's disclosure and its selective picking and choosing of information from the cited references in an effort to reconstruct the claimed methods is legally deficient and does not support the Office's conclusion of obviousness. *See In re Gorman*, 933 F.2d 982, 986, 18 U.S.P.Q.2d 1885, 1888 (Fed.Cir.1991).

Accordingly, Applicants submit that the subject matter of claims 1, 3-6, 12-15, and 22 could not have been obvious in view of the cited art. Applicants, therefore, request withdrawal of this rejection under Section 103(a).

Claims 8-11 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Schneider et al., Gormley et al., Prodromou et al., and in further view of Schulte et al. The Office contends that Schneider et al., Gormley et al., and Prodromou et al. do not teach the

inhibition of client proteins such as serine/threonine Raf-1, tyrosine kinase $p185^{erbB2}$, and mutant p-53 with Hsp90, but that Schulte et al. teaches the binding of geldanamycin to Hsp90 inhibits binding between Hsp90 and serine/threonine Raf-1, tyrosine kinase $p185^{erbB2}$, and mutant p-53.

Schulte et al. does not bridge the gap between the claimed invention and Schneider et al., Gormley et al., and Prodromou et al. as discussed above. Schulte et al. merely teaches the use of geldanamycin in contrast to the claimed use of a coumarin or a coumarin derivative and thus, does not render obvious the methods recited in claims 8-11. Therefore, the subject matter of claims 8-11 would not have been obvious in view of the cited art. Applicants, therefore, request withdrawal of this rejection under Section 103(a).

Claims 16-17 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Schneider et al., Gormley et al., Prodromou et al., and in further view of Hu et al. The Office contends that Schneider et al., Gormley et al., and Prodromou et al. do not teach hepatitis B virus reverse transcriptase and inhibition of the virus, but that Hu et al. teaches that Hsp90 is required for the activity of hepatitis B virus reverse transcriptase.

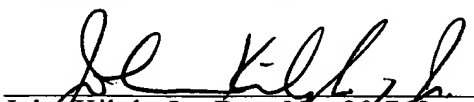
Hu et al, alone or in combination with Schneider et al., Gormley et al., and Prodromou et al does not cure the deficiencies of the cited art. There is no teaching or suggestion in Hu et al. that contacting Hsp90 with coumarin or a coumarin derivative would inhibit the activity of hepatitis B virus reverse transcriptase.

Therefore, the subject matter of claims 16-17 could not have been obvious in view of the cited art. Applicants, therefore, request withdrawal of this rejection under Section 103(a).

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Date: July 18, 2005